Heart failure oral therapies at discharge are associated with better outcome in acute heart failure: a propensity-score matched study

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Abstract: AIMS Heart failure oral therapies (HFOTs), including beta-blockers (BB), renin-angiotensin system inhibitors (RASi) and mineralocorticoid receptor antagonists, administered before hospital discharge after acute heart failure (AHF) might improve outcome. However, concerns have been raised because early administration of HFOTs may worsen patient's condition. We hypothesized that HFOTs at hospital discharge might be associated with better post-discharge survival. METHODS AND RESULTS The study population was composed of 19 980 AHF patients from the GREAT registry. The primary and secondary outcomes were 90-day and 1-year all-cause mortality, respectively. Survival was estimated with univariate and covariate-adjusted Cox proportional hazards regression models for the whole population and after propensity-score matching. HFOTs at discharge were consistently associated with no excess mortality in the unadjusted and adjusted analyses of the whole and matched cohorts. In the matched cohort, BB and RASi at discharge were associated with lower 90-day mortality risks compared to the respective untreated groups [hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.46-0.69; and HR 0.53, 95% CI 0.42-0.66, respectively]. The favourable associations of BB and RASi at discharge with 90-day mortality were present in many subgroups including patients with reduced or preserved left ventricular ejection fraction and persisted up to 1 year after discharge. The combination of RASi and BB was associated with an even lower risk of death than RASi or BB alone. CONCLUSIONS Administration of HFOTs at hospital discharge is associated with better survival of AHF patients.

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RESEARCH ARTICLE

Heart failure oral therapies at discharge are associated with better outcome in acute heart failure: a propensity-score matched study

Etienne Gayat[1,†*], Mattia Arrigo[1,2†], Simona Littnerova[3], Naoki Sato[4], Jiri Parenica[5], Shiro Ishihara[4], Jindrich Spinar[5], Christian Müller[6], Veli-Pekka Harjola[7], Johan Lassus[8], Òscar Miró[9], Aldo P. Maggioni[10], Khalid F. AlHabib[11], Dong-Ju Choi[12], Jin Joo Park[12], Yuhui Zhang[13], Jian Zhang[13], James L. Januzzi Jr[14], Katsuya Kajimoto[15], Alain Cohen-Solal[16], and Alexandre Mebazaa[1], on behalf of the GREAT Network

[1]Department of Anesthesiology and Critical Care, APHP – Saint Louis Lariboisière University Hospitals, University Paris Diderot and INSERM UMR-S 942, Paris, France; [2]Division of Cardiology, University Heart Center, University Hospital Zurich, Zurich, Switzerland; [3]Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic; [4]Division of Cardiology and Intensive Care Unit, Nippon Medical School Musashi-Kosugi Hospital, Kawasaki, Japan; [5]Department of Cardiology, University Hospital Brno and Medical Faculty, Masaryk University, Brno, Czech Republic; [6]Cardiovascular Research Institute Basel and Department of Cardiology, University Hospital Basel, Basel, Switzerland; [7]Emergency Medicine, Helsinki University and Helsinki University Hospital, Helsinki, Finland; [8]Division of Cardiology, Heart and Lung Center, Helsinki University and Helsinki University Hospital, Helsinki, Finland; [9]Emergency Department, Hospital Clinic and 'Emergencies: Processes and Pathologies' Research Group, IDIBAPS, University of Barcelona, Barcelona, Spain; [10]ANMCO Research Center, Florence, Italy; [11]Department of Cardiac Sciences, King Fahad Cardiac Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [12]Division Cardiology, Cardiovascular Center, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, South Korea; [13]Heart Failure Center Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [14]Division of Cardiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [15]Division of Cardiology, Sekikawa Hospital, Tokyo, Japan; and [16]Department of Cardiology, APHP – Lariboisière University Hospital, and INSERM UMR-S 942, Paris, France

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Aims Heart failure oral therapies (HFOTs), including beta-blockers (BB), renin–angiotensin system inhibitors (RASi) and mineralocorticoid receptor antagonists, administered before hospital discharge after acute heart failure (AHF) might improve outcome. However, concerns have been raised because early administration of HFOTs may worsen patient's condition. We hypothesized that HFOTs at hospital discharge might be associated with better post-discharge survival.

Methods and results The study population was composed of 19 980 AHF patients from the GREAT registry. The primary and secondary outcomes were 90-day and 1-year all-cause mortality, respectively. Survival was estimated with univariate and covariate-adjusted Cox proportional hazards regression models for the whole population and after propensity-score matching. HFOTs at discharge were consistently associated with no excess mortality in the unadjusted and adjusted analyses of the whole and matched cohorts. In the matched cohort, BB and RASi at discharge were associated with lower 90-day mortality risks compared to the respective untreated groups [hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.46–0.69; and HR 0.53, 95% CI 0.42–0.66, respectively]. The favourable associations of BB and RASi at discharge with 90-day mortality were present in many subgroups including patients with reduced or preserved left ventricular ejection fraction and persisted up to 1 year after discharge. The combination of RASi and BB was associated with an even lower risk of death than RASi or BB alone.

Conclusions Administration of HFOTs at hospital discharge is associated with better survival of AHF patients.

Keywords Acute heart failure • Prognosis • Oral therapy

*Corresponding Author. University Paris Diderot, Department of Anesthesiology and Intensive Care, INSERM UMR-S 942, Saint Louis – Lariboisière University Hospitals, 2 rue Ambroise Paré, 75010 Paris, France. Tel: +33 1 49958071, Fax: +33 1 49958073, Email: etienne.gayat@aphp.fr
†These authors contributed equally to this work.

Introduction

Acute heart failure (AHF) is a common and potentially fatal condition. The prognosis of AHF is poor, with a 5–8% rate of in-hospital mortality and 10% additional post-discharge mortality.[1–3] This immediate post-discharge period of risk usually lasts up to 90 days and is known as the 'vulnerable phase'.[4]

The pathophysiology of the vulnerable phase remains controversial. Some suggested a post-discharge increase in left ventricular filling pressure while other studies suggested underutilization of heart failure oral therapies (HFOTs) at discharge.[4] HFOTs, including beta-blockers (BB), renin–angiotensin system inhibitors (RASi: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) and mineralocorticoid receptor antagonists (MRA) have long been shown to markedly improve outcomes in stable heart failure (HF) with reduced left ventricular ejection fraction (HFrEF). Most recent European and North American HF guidelines recommend the maintenance and/or introduction of HFOT at hospital discharge in HFrEF, based on a few studies showing that BB withdrawal in AHF patients was associated with an increased risk of post-discharge death.[5–8] However, the maintenance or early introduction of HFOTs in patients who are fragile, still suffering or just recovered from the AHF crisis is sub-optimal, especially in old patients.[9,10] Data on the effect of the maintenance, introduction, and withdrawal of RASi and/or MRA, alone or combined with BB, during AHF hospitalization are therefore needed.

Moreover, since many AHF patients present with preserved left ventricular ejection fraction (HFpEF), no data exist whether HFOTs are beneficial in those patients. Despite demographic and clinical differences, the outcomes following AHF hospitalization in HFpEF patients are as poor as those in patients with HFrEF.[11] Due to negative trials,[12–15] recent European and North American HF guidelines recommended not administering oral medications either in chronic or, by extension, decompensated HFpEF patients.[5,8]

In the present study, we hypothesize that HFOTs at hospital discharge, whether alone or combined, might be associated with better outcomes (i) during the 'post-discharge vulnerable phase', and (ii) in all AHF patients, including those with HFpEF. Finally, as the maintenance, introduction and withdrawal of HFOT may be influenced by the severity of HF and/or of co-morbidities, their associations with post-discharge outcomes were assessed using propensity-matched cohorts.

Methods

Study population

The study population was derived from the GREAT registry, an international, multicentre, prospective observational cohort of 25 971 adult patients with AHF as the main diagnosis at hospital admission. Details on the constitution of the GREAT registry have been previously described in detail.[16,17] Acute HF includes both *de novo* HF and acutely decompensated HF as defined by the European Society of Cardiology (ESC) and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines.[5,7] The exclusion criteria for this study were mortality during index hospitalization, unknown vital status either at discharge or at 1-year follow-up and missing data on BB or RASi at discharge. To limit the heterogeneity of the results, patients included in small centres were also excluded from the study.

Following the inclusion and exclusion criteria, the study population comprised 19 980 AHF patients discharged alive from hospitals in 10 countries and two continents (France, Switzerland, Italy, Spain, Finland, Czech Republic, Saudi Arabia, China, Korea, Japan) for whom both medication at discharge and 1-year outcome were available (*Figure 1*).

Study outcomes

The primary outcome of the study was defined as 90-day all-cause mortality according to the prescribed HF therapies at hospital discharge. Three different classes of medication (BB, RASi and MRA) were considered. The secondary outcome was 1-year all-cause mortality according to the prescribed HF therapies at hospital discharge.

Statistical analysis

Survival was plotted with a Kaplan–Meier curve, and Cox proportional hazards regression models (univariate, covariate-adjusted and stratified for matched pairs after propensity-score matching) were used to estimate the associations between treatment regimen at discharge and the study outcomes. Given the observational nature of the data, treatment allocation was not randomly assigned in the study population and therefore we used propensity-score matching to reduce the risk of bias due to confounders, and the causal effects of the various treatment regimens on the outcomes could be more precisely estimated.[18] Each patient treated with a regimen was matched to one untreated control with a similar propensity score. Variables included in the propensity score model were selected from the available baseline variables based on known associations between treatment regimens and/or study outcomes: demographic characteristics [gender, age, body mass index, geographic region (Europe, Asia), medical history (arterial hypertension, diabetes mellitus, ischaemic heart disease, chronic HF, left ventricular ejection fraction (LVEF) >40%, atrial fibrillation, chronic obstructive pulmonary disease (COPD)], treatment at admission (BB, RASi, MRA, diuretics, vasodilators, aspirin, statin), biological indicators at admission [haemoglobin, sodium <136 mmol/L, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2], and haemodynamics at admission (systolic and diastolic blood pressure, heart rate). Treated and not treated patients were matched according to the nearest neighbor approach within a caliper width of 0.01. To assess the balance of covariates between the two groups before and after propensity-score matching, mean standardized differences (MSD) were used. A MSD <10% was considered to support the assumption of balance between groups. Subgroup analyses were performed in pre-specified subgroups according to age, sex, geographic region, LVEF, systolic blood pressure, heart rate, B-type natriuretic peptide (BNP), eGFR, sodium, history of HF, history of atrial fibrillation, history of COPD, type and cause of AHF, length of hospital stay, and prior treatment before hospital admission. The results are expressed as the median (interquartile range) or count (percentage) as appropriate. The risk of death of patients treated with a drug class, or a combination thereof ('treated') compared to patients not receiving the same drug class or combination ('untreated') is expressed as hazard ratio (HR) and 95% confidence interval (CI). A *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using R statistical software (The 'R' Foundation for Statistical Computing, Vienna, Austria) with the statistical package MatchIt for the matching process.

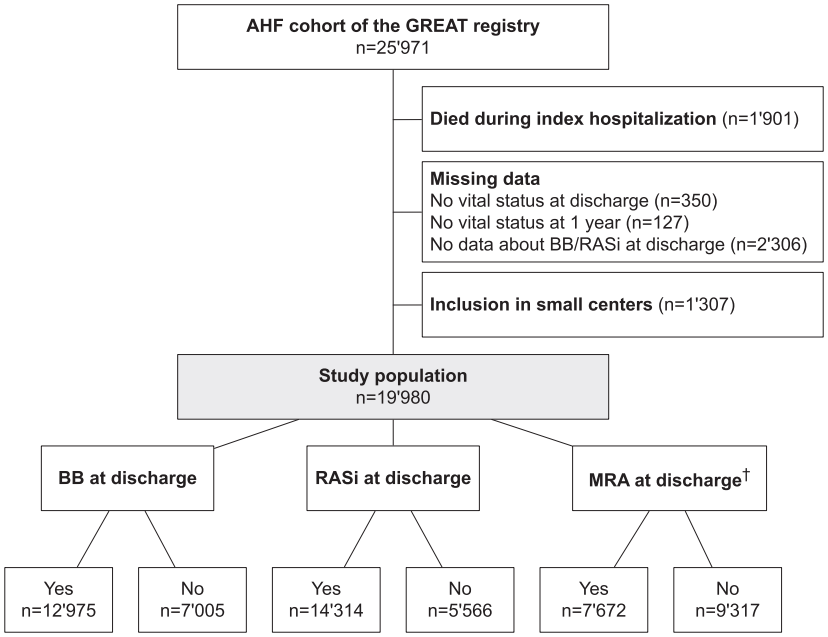

Figure 1 Flowchart of the study population. The study population consisted of a cohort of 19 980 acute heart failure (AHF) patients discharged alive for whom beta-blockers (BB) and renin–angiotensin system inhibitors (RASi) at discharge and 1-year outcome data were available. †Information about mineralocorticoid receptor antagonists (MRA) at discharge was lacking for 2991 included patients.

Results

Study population

The study population consisted of 19 980 AHF patients, predominantly men, with a median age of 72 (62–80) years and a high prevalence of cardiovascular risk factors. A substantial proportion (37%) of AHF patients had preserved ejection fraction (LVEF >40%), and ischaemic cardiomyopathy accounted for nearly half of all HF etiologies. The median BNP level at admission was 768 (383–1452) pg/mL. The baseline characteristics of the entire study population are summarized in *Table 1*. The median length of hospital stay was 10 (6–18) days. During the follow-up, the mortality rates at 90 days and 1 year were 7% and 16%, respectively.

At discharge, BB were prescribed to 12 975 patients (65%), RASi to 14 314 patients (72%), and a combination of BB and RASi to 10 443 patients (52%), whereas 3134 patients (16%) were treated with neither BB nor RASi (*Table 2* and Supplementary material online, *Table S1*). Mineralocorticoid receptor antagonists were prescribed to 7672 patients (45%). The baseline characteristics of patients according to their HF therapies at discharge are reported in the Supplementary material online, *Table S2*.

Effect of heart failure oral therapies at discharge on acute heart failure outcomes

The unadjusted and adjusted analyses of the whole and matched cohorts all show that BB, RASi or MRA at discharge were associated with no excess mortality at 90 days (*Figures 2–4* and Supplementary material online, *Tables S3* and *S4*).

Patients receiving BB at discharge had a lower 90-day mortality compared to BB-untreated patients (HR 0.72, 95% CI 0.65–0.80). Similarly, patients on RASi at discharge had a lower 90-day mortality than RASi-untreated patients (HR 0.52, 95% CI 0.47–0.58). Similar beneficial associations between BB and RASi at discharge and 90-day mortality were observed after covariate adjustments were performed (*Figure 2A* and Supplementary material online, *Table S3*). Conversely, no difference in 90-day mortality was found between patients treated or untreated with MRA (HR 1.00, 95% CI 0.89–1.12).

After propensity-score matching, the MSD of all covariates were reduced to below 10%, indicating an adequate covariate balance between BB-, RASi- and MRA-treated patients and their respective untreated patients (Supplementary material online, *Table S4* and *Figure S1*). In the matched cohorts, patients on BB at discharge (n=2819) had a lower 90-day mortality than BB-untreated patients (HR 0.56, 95% CI 0.46–0.69). A similar lower mortality was observed in patients on RASi at discharge (n=1919) compared to matched RASi-untreated patients (HR 0.53, 95% CI 0.42–0.66). In contrast, no difference in 90-day mortality was found in patients treated with MRA (n=3391) compared to matched MRA-untreated patients (HR 1.00, 95% CI 0.83–1.21).

Figure 2 illustrates the persistence of the favourable associations of BB and RASi at discharge with mortality beyond the first 90 days after discharge. Indeed, patients on BB (HR 0.62, 95% CI 0.55–0.71) and RASi (HR 0.62, 95% CI 0.53–0.72) at discharge had a lower 1-year mortality than matched patients who were not

Table 1 Baseline characteristics of the study population (*n*=19 980)

Medical history	
Female gender	8442 (42%)
Age, years	72 (62–80)
Body mass index, kg/m^2	25 (22–29)
Arterial hypertension	13 176 (66%)
Diabetes mellitus	8474 (43%)
Ischaemic cardiomyopathy	8695 (44%)
Chronic heart failure	8667 (44%)
LVEF >40%	6344 (37%)
Atrial fibrillation	5854 (31%)
BB at admission	8136 (41%)
RASi at admission	12 482 (63%)
MRA at admission	7961 (47%)
Diuretic at admission	9052 (56%)
Haemodynamics at admission	
Systolic blood pressure, mmHg	135 (115–159)
Diastolic blood pressure, mmHg	80 (67–90)
Heart rate, b.p.m.	89 (74–108)
Biology at admission	
Haemoglobin, g/L	137 (115–112)
Sodium >136 mmol/L	13 709 (70%)
Potassium, mmol/L	4.1 (3.9–4.6)
eGFR <60 mL/min/1.73 m^2	8213 (41%)
BNP, pg/mL	768 (383–1452)

BB, beta-blocker; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker).

treated with BB or RASi (HR 0.62, 95% CI 0.55–0.71; and HR 0.62, 95% CI 0.53–0.72, respectively). Conversely, no favourable association with 1-year mortality was found in patients treated with MRA compared to MRA-untreated patients (HR 0.97, 95% CI 0.86–1.10).

Effect of heart failure oral therapies at discharge on outcomes in various subgroups

Heart failure oral therapies at discharge, compared to matched untreated patients, showed no excess 90-day mortality in high risk AHF patients, including those with low natraemia, high BNP, advanced HF, impaired kidney function and a history of COPD. Similarly, no excess in 90-day mortality was observed when HFOTs were given at hospital discharge in patients whose length of stay was shorter than 7 days.

Figure 3 and Supplementary *Table S5* show a consistent association between receiving BB or RASi at discharge and reduced 90-day mortality in almost all study subgroups. Notably, favourable associations of BB and RASi at discharge with 90-day mortality were present in both classes of LVEF: HFrEF (HR 0.57, 95% CI 0.44–0.73; and HR 0.47, 95% CI 0.36–0.61, respectively) and HFpEF (HR 0.56, 95% CI 0.40–0.78; and HR 0.67, 95% CI 0.46–0.98, respectively) and in patients in whom HFOT was maintained (HFOT at admission) or introduced (no HFOT on admission). Though favourable, the associations between BB and RASi at discharge and short-term mortality were not statistically significant in AHF patients with low plasma BNP levels at admission or those with ischaemia or a history of COPD. In patients with impaired renal function, RASi at discharge also showed no association with short-term mortality.

Patients treated with MRA at discharge, compared to matched patients untreated with MRA, showed no excess in 90-day mortality in all study subgroups except a non-significant increased risk of death in patients with atrial fibrillation. Interestingly, the subgroup of patients with HFpEF, but not HFrEF, showed a positive association between oral MRA at discharge and 90-day mortality (HR 0.70, 95% CI 0.49–0.99).

Combination of heart failure oral therapies at discharge and outcome in acute heart failure

Because receiving BB or RASi at discharge, but not MRA, had marked favourable associations with the outcome, we tested the association of the combination of BB and RASi with post-discharge outcomes. *Figure 4A* and *B* show an additionally lower 90-day mortality of patients treated with a combination of RASi and BB (*n*=1178) compared to matched patients treated with BB alone (HR 0.47, 95% CI 0.34–0.64). *Figure 4A* and *C* further show the benefits on 90-day mortality of the combination of BB and RASi (*n*=1876) compared to matched patients treated with RASi alone (HR 0.75, 95% CI 0.57–0.99). The favourable association of combined BB and RASi with the reduced risk of death remained substantial up to 1 year after the acute episode: patients treated with RASi on top of BB and patients treated with BB on top of RASi had a lower 1-year mortality than their respective matched patients treated with BB or RASi alone (HR 0.64, 95% CI 0.52–0.79; and HR 0.72, 95% CI 0.60–0.85, respectively).

Figure 4D further shows the striking difference in 1-year mortality between patients receiving dual therapy (BB and RASi), BB or RASi alone and those not treated with either BB or RASi at discharge in the entire AHF cohort. Patients with AHF receiving neither BB nor RASi at discharge had a striking excess in 90-day mortality (10.6%) compared to patients on full HFOT at discharge (3.2%) (*Figure 4D*).

Discussion

The global pandemic of HF represents a medical and financial priority in the modern healthcare system. However, while standard management is articulated in clinical practice guidelines, surprisingly few data exist regarding the optimal application of drug therapies, treatment goals are frequently not met, and standards for treating HFpEF (accounting for up to half of global HF cases) are not established. One of the obstacles limiting the early prescription of HFOTs at discharge from HF hospitalization might be related to the adverse effects of these drugs while patients are still fragile.

Table 2 Baseline characteristics of the study population according to heart failure oral therapies at discharge (*n*=19 980)

	BB and RASi (*n*=10 443)	BB only (*n*=2532)	RASi only (*n*=3871)	No BB/No RASi (*n*=3134)	*P*-value
Demographics					
Female gender	4044 (39%)	1063 (42%)	1903 (49%)	1431 (46%)	<0.001
Age, years	70.3 (60–79)	71.9 (61–80)	76 (66–83)	72.8 (61–81)	<0.001
Body mass index, kg/m^2	26.1 (23–30)	25.1 (22–29)	24.3 (22–28)	23.8 (21–27)	<0.001
Medical history					
Arterial hypertension	7252 (70%)	1569 (62%)	2642 (69%)	1713 (55%)	<0.001
Diabetes mellitus	4466 (43%)	1049 (42%)	1442 (37%)	987 (32%)	<0.001
Ischaemic heart disease	5124 (49%)	1136 (45%)	1360 (36%)	1215 (39%)	<0.001
Chronic heart failure	4692 (46%)	1184 (47%)	1609 (43%)	1182 (38%)	<0.001
LVEF >40%	2940 (31%)	884 (38%)	1337 (46%)	1127 (48%)	<0.001
Atrial fibrillation	2842 (28%)	810 (33%)	1300 (35%)	902 (29%)	<0.001
Treatment at admission					
BB	5457 (53%)	1482 (59%)	582 (15%)	488 (19%)	<0.001
RASi	7879 (75%)	358 (14%)	3208 (83%)	745 (24%)	<0.001
MRA	2574 (28%)	606 (28%)	823 (25%)	497 (18%)	<0.001
Diuretic	5062 (54%)	1289 (57%)	1664 (57%)	1037 (58%)	0.002
Biology at admission					
Hemoglobin, g/L	13 (11.4–14.4)	12.3 (10.6–13.9)	12.3 (10.8–13.8)	12.4 (10.7–13.9)	<0.001
Sodium >136 mmol/L	7207 (71%)	1686 (67%)	2699 (72%)	2044 (68%)	<0.001
eGFR <60 mL/min/1.73 m^2	4476 (43%)	847 (34%)	1533 (40%)	1270 (42%)	<0.001
BNP, pg/mL	826 (428–1500)	772 (388–1460)	661 (307–1261)	700 (332–1499)	<0.001
Haemodynamics at admission					
Systolic blood pressure, mmHg	138 (117–160)	130 (110–150)	140 (120–160)	127 (110–147)	<0.001
Diastolic blood pressure, mmHg	80 (70–93)	76 (65–88)	80 (68–90)	73 (62–84)	<0.001
Heart rate, b.p.m.	90 (75–110)	89 (74–109)	88 (72–107)	85 (72–103)	<0.001

BB, beta-blocker; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker).

Accordingly, we sought to examine potential benefits of pharmacological treatments indicated in HFrEF on post-discharge outcomes using a large, intercontinental AHF registry.

In this study, we found that treatment with oral BB, RASi and MRA should be maintained or introduced before hospital discharge in AHF patients. Maintenance or introduction of HFOT may be challenging in AHF, as patients are admitted with dyspnoea and other signs and symptoms including altered heart rate and/or blood pressure and often deteriorated kidney and/or liver function. When AHF patients survive and recover from this acute phase and become stable, the introduction of HFOT may still be challenging, as the time available to optimize HF therapy may be short due to financial penalties incurred when a hospital stay exceeds a certain number of days. Hence, physicians may hesitate to introduce HFOT before hospital discharge. The present study shows that all HFOTs should be introduced early in all study subgroups, including those with a high risk of poor outcomes, ideally before discharge, or in case of persistent instability as soon as possible during the following outpatient visits.

Our study showed that 90-day mortality of AHF patients was three times greater in patients who did not receive HFOT at discharge compared to those with full HFOT. While rapid and beneficial effects of oral BB on mortality in chronic HF are well-established, their benefits are less well known following hospitalization for AHF. Limited data suggest that the continuation or administration of BB during the index hospitalization is associated with improved short-term survival.[19,20] Furthermore, a very recent meta-analysis by Prins and colleagues showed detrimental effects of BB discontinuation on short-term mortality in patients admitted with AHF.[21] The present study, by reducing allocation bias through propensity-score matching, did not find any signal of harm and conversely shows 40% lower rates in both short-term and 1-year mortality in patients treated with oral BB before hospital discharge compared to patients untreated with oral BB at discharge. Similarly, our study also shows a 40% lower risk of both short- and long-term post-discharge risk of death associated with the use of oral RASi in AHF. Fonarow and coworkers previously reported a trend toward reduced short-term mortality associated with oral RASi treatment at hospital discharge; however, the process–outcome link lost significance after propensity adjustment.[22] Perhaps more notably, we found that combined therapy with BB and RASi was associated with a lower mortality than BB or RASi alone, with an additional 25–50% lower risk of short- and long-term mortality. In summary, patients who are not receiving HFOT at discharge are strikingly 'vulnerable' in the post-discharge phase.

Our study showed that oral MRA at discharge was neither associated with excess mortality nor with a favourable association with

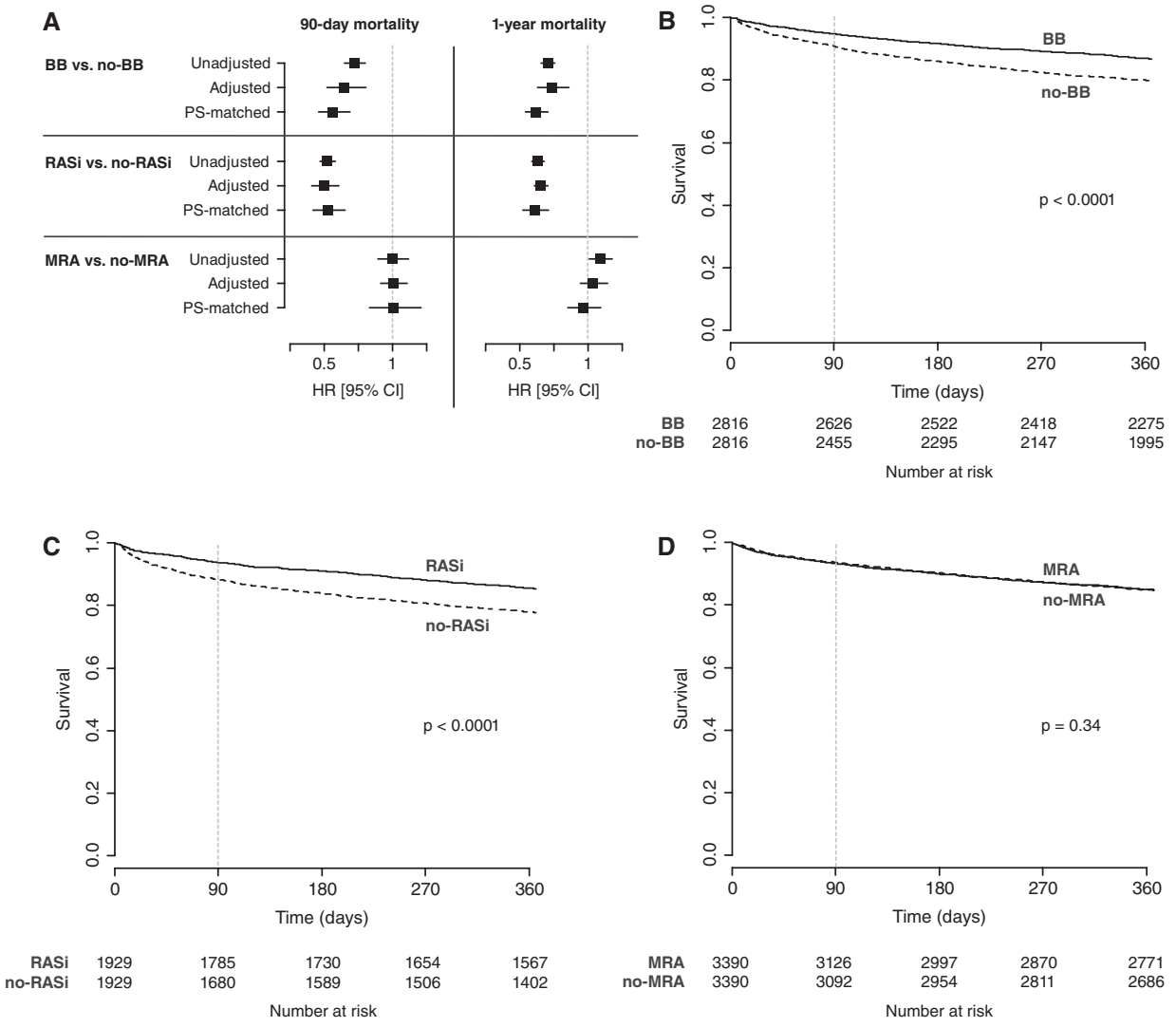

Figure 2 Survival according to treatment at discharge in the matched cohort. Panel *A* shows the hazard ratios (HR) and 95% confidence intervals (CI) of the unadjusted, adjusted and propensity score (PS)-matched models for 90-day and 1-year mortality according to treatment at discharge. Panels *B*–*D* illustrate the survival of treated patients (continuous line) and PS-matched untreated patients (dotted line) for beta-blockers (BB) (*A*, *n*=5638), renin–angiotensin system inhibitors (RASi: angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) (*B*, *n*=3838), and mineralocorticoid receptor antagonists (MRA) (*C*, *n*=6782).

post-discharge outcome, except for the subgroup of AHF with preserved LVEF. The lack of favourable association between oral MRA at discharge and outcome contrasts with the beneficial associations seen with oral BB and/or RASi at discharge and with previous trials showing marked reductions in long-term mortality associated with MRA treatment in stable chronic HFrEF patients.[23–25] However, our results are derived from a 'real-world' cohort, a completely different setting from that of trials, and are in line with other recent 'real-world' studies reporting modest (if any) effects of spironolactone on mortality in HF, especially in mild forms.[26–29] A possible explanation for the lack of benefit of MRA might be related to the occurrence of severe hyperkalaemia in MRA-treated patients.[26–29] Thus, the failure of MRA to show a beneficial effect could have been related to a higher incidence of drug discontinuation due to hyperkalaemia. The potential availability of new potassium-lowering agents could increase MRA persistence and then result in a more favourable outcome. We acknowledge that our registry did not distinguish between the two recommended MRA (spironolactone or eplerenone); however, we assume that the vast majority of MRA-treated patients in our study received spironolactone. Our results do not in any way refute the benefits of MRA therapy in patients with stabilized chronic HF; rather, they suggest that in the early days following AHF, its benefit is less clear. More data regarding the use of MRA in AHF are needed.

The subgroup analysis further showed favourable associations between oral BB and RASi at discharge and short-term outcomes

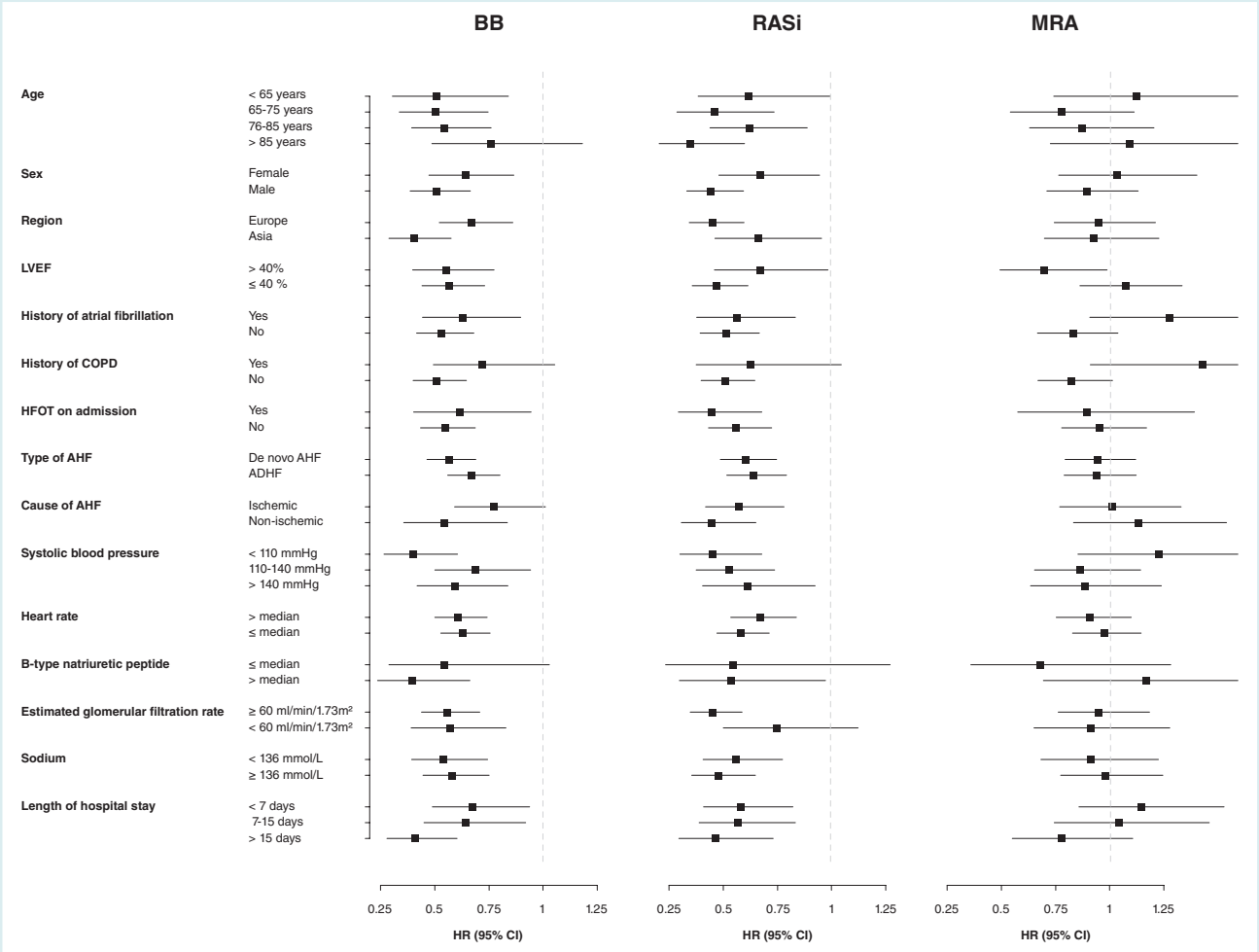

Figure 3 Subgroup analyses for 90-day mortality. AHF, acute heart failure; BB, beta-blockers; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HFOT, heart failure oral therapy; HR, hazard ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; RASi, renin–angiotensin system inhibitors (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker). ADHF, acute decompensated heart failure.

in almost all study subgroups, including those with a short hospital length of stay, patients from Europe or Asia, and surprisingly in patients with both reduced or preserved LVEF. The subgroup analysis further showed a unique favourable association between oral MRA at discharge and short-term outcomes in AHF with preserved LVEF (defined as LVEF ≥40%, which includes also the 'mid-range' group according to the most recent ESC guidelines). This is clearly intriguing, as all HF therapies have been shown to reduce long-term mortality of chronic stable HFrEF, but not HFpEF, patients. One might speculate that the pathophysiological imbalances during the vulnerable post-discharge phase, including neurohumoral activation and myocardial ischaemia, may, at least in part, be reduced by treatment with BB and RASi through similar mechanisms in HFrEF and HFpEF patients.[4] Heart failure oral therapy might also improve some co-morbidities in HFpEF patients. Accordingly, our data favour the use of full HFOT at discharge in all AHF patients.

Heart failure incidence and prevalence are rising, in part due to the improvement in care of other cardiovascular and non-cardiovascular illnesses and argues for a global effort toward the improved diagnosis and management of HF.[30] Unfortunately, it remains quite clear that the ability of healthcare providers and patients alike to recognize the symptoms/signs of HF and to ensure quality care is limited. There is not a more important time to establish quality care than in the period following hospitalization for AHF, as this represents a 'vulnerable period' associated with a substantial risk of downward decline, readmission, and death. Optimizing how patients are managed at this pivotal moment is clearly a priority: with global rates of the incidence and prevalence of HF on the rise, the associated morbidity, mortality, and costs associated with the diagnosis are expected to increase exponentially, potentially overwhelming the global healthcare system. Therefore, the importance of our results is clear: through careful analyses, we found that full HFOT at discharge is associated with a consistent reduction in mortality in patients with recent AHF, regardless of LVEF or the presence of co-morbidities. In light of the widespread availability and inexpensive nature of BB and RASi, our results have substantial

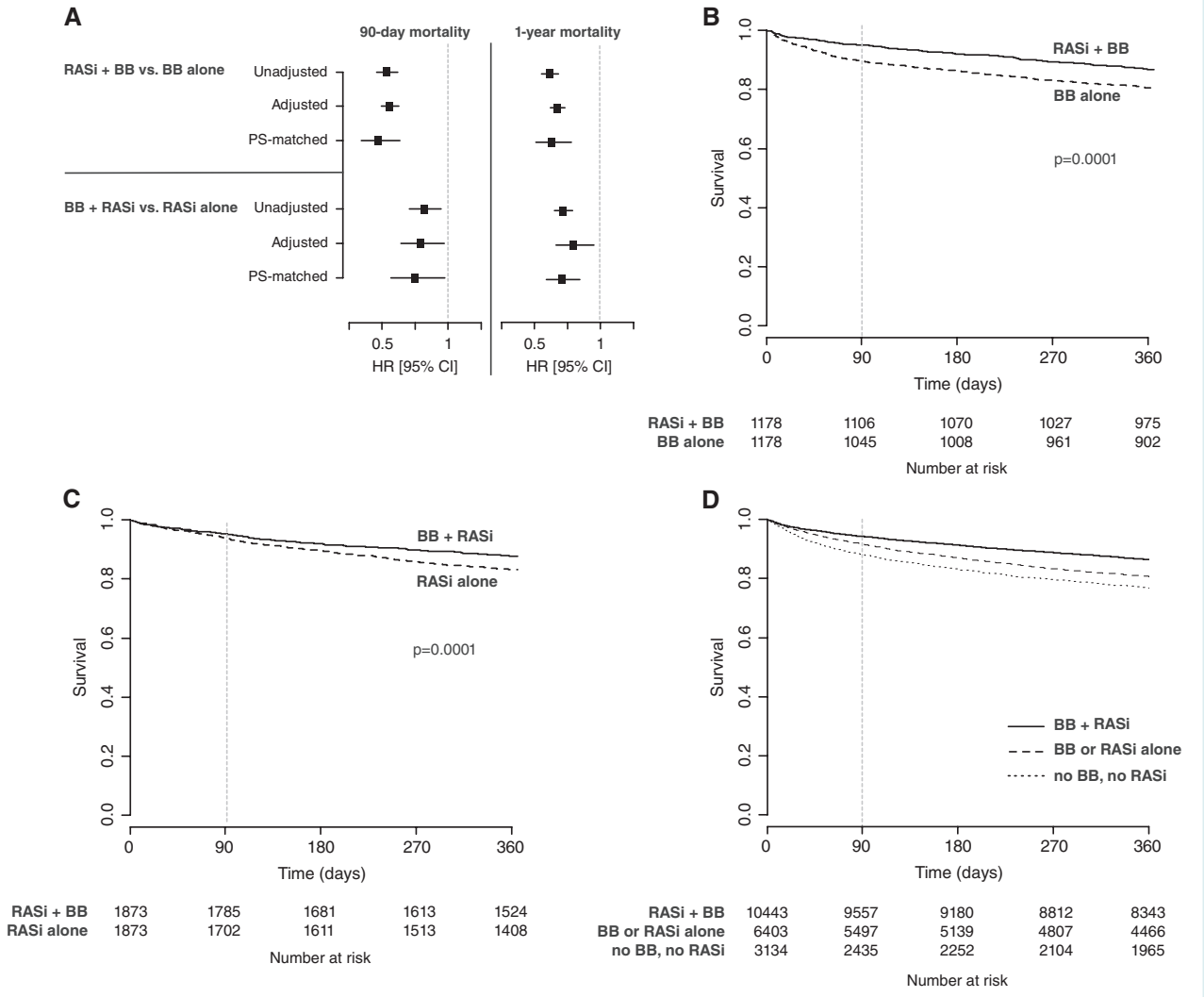

Figure 4 Survival according to combined treatment at discharge. Panel *A* shows the hazard ratios (HR) with 95% confidence intervals (CI) of the unadjusted, adjusted and propensity score (PS)-matched models for 90-day and 1-year mortality according to combinations of beta-blockers (BB) and renin–angiotensin system inhibitors (RASi: angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) at discharge. Panel *B* illustrates the survival of patients treated with RASi on top of BB (continuous line) and PS-matched patients treated with BB alone (dotted line) (n=2356). Panel *C* illustrates the survival of patients treated with BB on top of RASi (continuous line) and PS-matched patients treated with RASi alone (dotted line) (n=3752). Panel *D* illustrates the survival of all study patients (n=19 980) according to the treatment regimen: patients with dual treatment (receiving a combination of BB and RASi), partial treatment (receiving either BB or RASi alone) or no treatment (neither BB nor RASi).

global health implications: administering a combination of at least oral BB and RASi in all patients with AHF appears justified. As the care of hospitalized AHF patients is typically not in the hands of cardiology specialists,[31] our data are applicable to a broad range of medical caregivers globally.

Limitations

The present study has several limitations. Firstly, it was a non-randomized study. The effects of a drug intervention and its safety can be shown only by randomized, prospective trials. Thus, no firm implications with respect of a causal role between treatment and outcomes can be driven by the present analysis. However, propensity score methodology allowed us to balance groups according to variables that were recorded in the GREAT registry, reflecting the experience of daily clinical practice in tertiary centres in Europe and Asia. Despite the large number of included variables, other factors associated with the administration of a specific treatment (e.g., frailty, dementia, haemodynamics, persistent instability at discharge or dosing of chronic medications) may not have been included in the propensity score and might result in a bias in the estimates of treatment effectiveness.

Therefore, a healthy user bias cannot completely be ruled out. However, missing variables would unlikely interfere with the consistent results of 40% improvement in risk of death consistently observed in unmatched and matched, unadjusted and adjusted populations and in many study subgroups, which strongly suggest that the combination of BB and RASi at discharge is associated with marked benefits in AHF. We further acknowledge that this study did not consider temporary discontinuation of HFOTs during hospitalization nor assess the administered dose of HF therapies at discharge or changes in HFOT during follow-up. Changes in the treatment regimen (including withdrawal or introduction) after hospital discharge might confound the outcomes, especially long-term mortality. However, previous data showed that HFOTs prescribed during hospitalization for AHF are often not changed during the subsequent months.[10,32] We also did not examine the effects of newer HFOTs (such as ivabradine or sacubitril/valsartan) or devices on survival. A recent study suggests beneficial effects of maintaining ivabradine at discharge on short-term outcome in hospitalized HF patients.[33] Further prospective, randomized trials should confirm our present results. As data on black AHF patients are missing in the present study, future trials should address that population. The present study also did not address the effect of HFOT at discharge of AHF on hospital readmission because the GREAT registry did not report data about subsequent hospitalizations. Given these limitations, prospective trials are needed.

Conclusions

Our study showed that administration of HFOT at hospital discharge is associated with better survival of AHF patients regardless of left ventricular systolic function or associated co-morbidities.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Use of beta-blockers and renin–angiotensin system inhibitors at admission and discharge.

Table S2. Baseline characteristics and mean standardized differences before propensity-score matching.

Table S3. Mortality risk according to treatment at hospital discharge.

Table S4. Baseline characteristics and mean standardized differences after propensity-score matching.

Table S5. Subgroup analyses for 90-day mortality.

Figure S1. Mean standardized differences before and after propensity-score matching.

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